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# NORTHSTAR HEALTHCARE CONSULTING CLINICAL COMPASS

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## DRUGS AND LIVER DISEASE

### INTRODUCTION

Chronic liver disease accounts for over 27,000 deaths per year and is the 12<sup>th</sup> leading cause of death in the U.S. Hepatitis C viral infection is the most frequent cause of chronic liver disease and the most common indication for liver transplantation. Other etiologies of chronic liver disease include hepatitis B viral infection as well as autoimmune, alcoholic, nonalcoholic (fatty) and drug-induced liver diseases. In the U.S., drug-induced liver disease is the leading cause of liver failure. Recognizing

and preventing drug-induced liver disease continue to be the most important management approach since treatment for most drug-induced liver disease is not effective.



Late-stage progressive liver disease, known as cirrhosis, is distinguished by fibrosis and abnormal nodules resulting in severe complications of end-stage liver disease, such as ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and hepatic encephalopathy. The only curative treatment for decompensated disease is liver transplantation.

### LIVER DISEASE SCORING SYSTEMS

Two scoring systems are used to determine the severity of liver disease.

#### *Child-Pugh Score*

The Child-Pugh scoring system is used to determine the outcome of surgery in cirrhotic patients, assess the severity and prognosis of chronic liver disease and to stratify patients listed for liver transplantation. The Child-Pugh score accounts for total bilirubin, serum albumin, prothrombin time, ascites and hepatic encephalopathy. These variables were selected because each marker assesses the function of the liver and, as a whole, the variables are markers of the multiorgan

changes that result from cirrhosis. The Child-Pugh score and interpretation of the score are highlighted in the tables below (Table 1 and 2).

**Table 1: Child-Pugh Score**

Variable	1 Point	2 Points	3 Points
Total bilirubin (mg/dL)	<2	2-3	>3
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (seconds, INR)	<4 (<1.7)	4-6 (1.7-2.2)	>6 (>2.2)
Ascites	None	Suppressed	Refractory
Hepatic encephalopathy	None	Grade I-II (or suppressed)	Grade III-IV (or refractory)

PT=prothrombin time; INR=international normalized ratio

**Table 2: Child-Pugh Score Interpretation**

Points	Class	Life Expectancy	Perioperative Mortality (%)	One-Year Survival (%)	Two-Year Survival (%)
5-6	A	15-20 years	10	100	85
7-9	B	Candidate for transplant	30	81	57
10-15	C	1-3 years	82	45	35

The Child-Pugh scoring system is also used to determine medication dose adjustments in patients with hepatic dysfunction. Limitations of this tool include subjective assessments (degree of ascites and hepatic encephalopathy) and cut-off points for continuous variables (bilirubin and albumin) are arbitrary. The accuracy of the scoring system may be improved with the inclusion of markers, such as serum creatinine, that have shown to impact the prognosis of liver disease and additional markers that assess the severity of disease, such as portal hypertension and esophageal varices. Despite these limitations, the Child-Pugh score continues to be used bedside due to convenience and accounts for specific clinical markers of the disease.

#### *Model for End-Stage Liver Disease*

The model for end-stage liver disease (MELD) was designed to evaluate the prognosis of patients with cirrhosis undergoing transjugular portosystemic intrahepatic shunt (TIPS) and is used to assess the severity of liver disease. The MELD score includes bilirubin, creatinine, international normalized ratio (INR) and cause of liver disease. Limitations to the MELD scoring system consist of significant variations in objective laboratory values (bilirubin, creatinine and INR) due to varying laboratory methodologies or rapid change in the patient's clinical course. The MELD score may also be influenced by the medical management of the patient. In addition, calculating the MELD score requires logarithmic computation that may not be quickly performed at bedside. Thus, experts recommend using the MELD scoring system for patients waiting for liver transplantation and the scoring system is used by the United Network for Organ Sharing in prioritizing livers.

## **DRUG-INDUCED LIVER DISEASE**

Drug-induced liver disease (DILD) is the leading cause of acute liver failure in patients referred for liver transplantation in the U.S. The incidence of reported DILD is low, ranging from 1 in 10,000 to

1 in 100,000 for most drugs; however, the exact incidence is hard to determine due to underreporting and difficulty in diagnosing DILD. Adults are generally at a higher risk compared to children and women are usually affected more than men. Additional DILD risk factors involve malnutrition, alcohol use, obesity, pregnancy, concomitant medications, drug interactions and genetic predisposition, which impact drug metabolism and clearance.

Numerous drugs are associated with DILD; yet, in most circumstances, there is no effective treatment besides discontinuing the offending drug and providing supportive care. The only useful methods of improving outcomes in patients include identification and prevention of DILD. Table 3 lists examples of risk factors and drugs associated with DILD.

**Table 3: Examples of Drug-Induced Liver Disease Risk Factors and Associated Drugs**

Risk Factors	Drugs
Female	nitrofurantoin, sulfonamides
Male	azathioprine, amoxicillin/clavulanate
Older age	isoniazid, amoxicillin/clavulanate
Younger age	valproic acid
Chronic alcohol abuse	acetaminophen, isoniazid, methotrexate
Malnutrition	acetaminophen
Pregnancy	isoniazid
Diabetes	methotrexate
Chronic liver disease	methotrexate, niacin
Chronic kidney disease	allopurinol
HIV infection	dapsone, trimethoprim/sulfamethoxazole
Hepatitis B or C infection	antiretroviral agents, antituberculosis agents
Genetic predisposition	phenytoin, sulfonamides, isoniazid, anticonvulsants

#### *Types of Drug Reactions*

Intrinsic drug reactions are predictable and usually are dose-related and occur after a short time of exposure to the drug; however, most DILD drug reactions are idiosyncratic, unpredictable, not dose-related and associated with variable latency periods, expanding a few days to months. Environmental and genetic factors may be involved in a patient's susceptibility to a drug. An allergic or nonallergic drug reaction may cause DILD to be unpredictable. Drug reactions including clinical characteristics of rash, fever, eosinophilia and recurring positive challenge are usually attributed to hypersensitivity, which typically occur 1 to 5 weeks after drug exposure. The characteristics of hypersensitivity are absent in nonallergic idiosyncratic drug reactions and hepatotoxic metabolites are usually the culprit for the liver disease.

#### *Classifications*

All forms of acute and chronic liver disease can result from DILD and clinical features of DILD range from asymptomatic increases in liver enzymes to acute liver failure. The types of DILD consist of hepatocellular, cholestatic, mixed pattern, chronic hepatitis, granulomatous hepatitis, hepatic venous occlusion, steatosis, phospholipidosis, and neoplastic lesions.

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The most common type of DILD is acute hepatocellular injury, defined as an elevation in alanine aminotransferase (ALT) greater than 2 times above the upper limit of normal (ULN). Symptoms of acute hepatocellular injury are jaundice, fatigue, anorexia and nausea and associated drugs include acetaminophen, valproic acid, nefazodone, venlafaxine and lovastatin.

Acute cholestasis is associated with the reduction in bile flow due to decreased secretion or obstruction of the biliary tree, is defined as an isolated increase in alkaline phosphatase (AP) 2 times above the ULN and patients usually present with jaundice, pruritis, pale stool and dark urine. Drugs associated drugs include amoxicillin/clavulanate, erythromycin, carbamazepine, chlorpromazine and anabolic steroids.

Acute hepatic injury with mixed pattern can be primarily hepatocellular with cholestatic features or primarily cholestatic with hepatocellular features. Concentrations of aspartate aminotransferase (AST) and ALT are more than 8 times the ULN, AP concentrations are greater than 3 times the ULN and an ALT/AP ratio of 2-5 characterize mixed pattern hepatic injury. Patient features include jaundice and biliary obstruction symptoms. Causative drugs include nonsteroidal antiinflammatory drugs (NSAIDs), macrolides, nitrofurantoin, sulfonamides, amoxicillin/clavulanate, cyclosporine and carbamazepine.

Drug-induced chronic hepatitis resembles autoimmune hepatitis, including clinical features of jaundice, anorexia, fatigue, enlarged liver, splenomegaly and ascites, and usually occurs after prolonged exposure (several months to years) to the drug. Elevations in aminotransferases and coagulation markers are also present. Dantrolene, methyldopa, minocycline, nitrofurantoin and sulfonamides can cause chronic hepatitis.

Hepatic vascular injuries, such as hepatic vein thrombosis and hepatic venous occlusion, may occur after exposure to large doses of drugs over a short period of time or after exposure to small doses of drugs over a prolonged period of time. Clinical presentation includes hepatomegaly, abdominal pain, ascites, jaundice and portal hypertension. Causative drugs of hepatic vascular injury include etoposide, vincristine, vinblastine, cyclophosphamide and mitomycin.

Other types of DILD include granulomatous hepatitis, steatosis, phospholipidosis and neoplastic lesions. Granulomatous hepatitis generally occurs between 10 days to 4 months after initiation of drug therapy and symptoms may include fever, diaphoresis, malaise, anorexia, jaundice and splenomegaly. Steatosis results from prolonged use of the offending drug and can be benign or progress to cirrhosis, chronic liver failure and hepatic necrosis. Phospholipidosis can also result after prolonged drug (amiodarone) exposure and patients may present with hepatomegaly, neuropathy, pulmonary manifestations and thyroid disorders. Neoplastic lesions have been associated with oral contraceptives and anabolic steroids.

## **DRUG DOSING AND CONSIDERATIONS IN LIVER DISEASE**

The liver is key in drug metabolism and clearance and in chronic liver disease, physiologic changes can occur to the liver, affecting the function of the liver and thus the degree and extent of drug metabolism and clearance. Several factors can influence the effect of liver disease on drug

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metabolism and clearances, such as disease severity and type, enzymes involved in the metabolism of drugs, blood flow, number of functioning hepatocytes and pharmacokinetic drug properties.

Most hepatically-metabolized drugs can be used safely in patients with chronic liver disease when dosages are adjusted appropriately. Generally, initial and maintenance doses should be reduced and serum drug levels monitored to prevent hepatotoxicity in patients with liver disease. Caution should be used with drugs that are metabolized by the liver, increase sodium and water retention, precipitate hepatic encephalopathy, have an increased risk for drug interactions and are highly protein bound. Examples of drugs that should be used cautiously in patients with liver disease include phenytoin, valproate, theophylline, corticosteroids, NSAIDs, benzodiazepines, opioids, aminoglycosides and fluoroquinolones.

Drugs that can result in dose-dependent hepatotoxicity, such as acetaminophen, aspirin, isoniazid, methotrexate and valproate should be avoided in patients at an increased risk for hepatotoxicity. Drugs that are not a prodrug are usually preferred over prodrugs since non-prodrugs do not require activation by the liver. Renally-excreted drugs or drugs metabolized via hepatic glucuronidation instead of oxidation may be better choices in patients with liver disease.

## CONCLUSION

Chronic liver disease is associated with various etiologies, including medication use. The only effective treatment for drug-induced liver disease in most situations is to discontinue the offending drug and provide supportive care. Identification and prevention remain important management strategies in patients with hepatotoxicity. Medication use in patients with liver disease poses challenges for clinicians, especially since there is no indicator to assess the ability of the liver to metabolize drugs.

The therapeutic benefit should outweigh the risk of toxicity when selecting drugs for patients with liver disease. When possible, the choice should include drugs that are cleared by the kidneys, metabolized by the liver via glucuronidation and/or are not prodrugs. Drugs that are inherently hepatotoxic should be avoided in patients at an increased risk for hepatotoxicity. When drug therapy is needed in patients with liver disease, initiate with a reduced dose, monitor the patient and titrate cautiously until the therapeutic response is achieved or an adverse reaction appears.

## REFERENCE

Kim JW, Phongsamran PV. Drug-induced liver disease and drug use considerations in liver disease. *J Pharm Prac.* 2009;22(3):278-89.